

1/7/11

AMENDMENTS TO THE SPECIFICATION

Please amend the paragraph beginning on page 62, line 13, as follows:

Step 720. In optional step 720, a determination is made as to whether the cellular constituents in the candidate causative cellular constituent set are druggable. Hopkins and Groom, 2002, Nature Reviews 1, p. 727 provide one definition of a druggable target. To develop a definition of a druggable genome, Hopkins and Groom identified the molecular targets to rule-of-five compliant compounds. As put forth by Lipinski *et al.*, 1997, Adv. Drug Deliv. Rev. 23,3, a rule-of-five compliant synthetic compound (*e.g.*, compounds other than those derived from natural products) has less than five hydrogen-bond donors, the molecular mass of the compound is less than 500 Daltons, the lipophilicity is less than 5, and the sum of the nitrogen and oxygen atoms is less than 10. A thorough review of the literature by Hopkins and Groom identified 399 non-redundant molecular targets that have been shown to bind rule-of-five compliant compounds with binding affinities below 10 μ M. Next, Hopkins and Groom took the drug-binding domains of the 399 non-redundant molecular targets and determined the families that they represent, as captured by their InterPro domain (Hopkins and Groom, 2002, Nature Reviews 1, p. 727; Apweiler *et al.*, 2001, Nucleic Acids Res. 29,37). A total of 130 protein families represent the 399 non-redundant molecular targets. These protein families are provided in the online supplemental information for Hopkins and Groom, 2002, Nature Reviews Drug Discovery 1, p. 727 at ~~nature.com/reviews/drugdisc~~ the "nature" website with the extension ".com/reviews/drugdisc" and include G-protein coupled receptors, serine/threonine and tyrosine protein kinases, zinc metallo-peptidases, serine proteases, nuclear hormone receptors and phosphodiesterases. Thus, in one embodiment of the present invention step 720 comprises determine whether each cellular constituent in the candidate causative cellular constituent set includes a druggable domain as defined by Hopkins and Groom.